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ACUTE SENSITIVITY AND TOLERANCE TO ALCOHOL AS PREDICTORS OF AT-RISK DRINKING

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ACUTE SENSITIVITY AND TOLERANCE TO ALCOHOL AS PREDICTORS OF AT-RISK DRINKING

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
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By

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ABSTRACT OF THESIS

ACUTE SENSITIVITY AND TOLERANCE TO ALCOHOL AS PREDICTORS OF AT-RISK DRINKING

Laboratory studies have reliably shown that reduced sensitivity to alcohol's subjective intoxicating effect is associated with heavier drinking. More recently, there has been research to suggest that heightened sensitivity to the disinhibiting effects of alcohol might also contribute to at-risk drinking. Most research on the acute effects of alcohol has focused on drinking magnitudes averaged across participants with little attention to how individual differences influence abuse potential. This study overcomes previous limitations by testing the degree to which individual differences in acute sensitivity and tolerance to the subjective intoxicating and disinhibiting effects of alcohol predict drinking behavior in a large sample size. Data from six laboratory studies were aggregated to comprise a sample of 200 adults. Participants' level of subjective intoxication and disinhibition were assessed following 0.65 g/kg alcohol once during the ascending limb of the blood alcohol concentration (BAC) curve and again at the same BAC during the descending limb. The measures were also assessed following placebo. Alcohol increased subjective intoxication and disinhibition. At-risk drinking was predicted by low sensitivity to subjective intoxication on the ascending limb and reduced acute tolerance overall. These data suggest that individual variability in subjective intoxication and persistent disinhibition are key predictors of abuse potential.

KEYWORDS: Subjective Intoxication, Disinhibition, Sensitivity, Tolerance, Go/no-go Task

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April 27, 2020

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Introduction

Tolerance in relation to alcohol refers to a diminished response to the drug as doses are repeated (American Psychiatric Association, 2013). Alcohol tolerance is a marker of and one of the diagnostic criteria for alcohol use disorder (AUD) as it encourages increasing the quantity of alcohol consumed to reach a desired level of intoxication (American Psychiatric Association, 2013).

Many studies over the past fifty years have examined alcohol tolerance by comparing behavioral effects of alcohol in heavy or moderate drinkers with those who abstain from alcohol. Tolerance has been seen in a variety of behavioral and cognitive responses including sensory, motor, and psychological responses (Goldberg, 1943; LeBlanc, Gibbins, & Kalant, 1973; Mitchell, 1985). A seminal study by Goldberg (1943) showed that, under the same dose of alcohol, heavy drinkers displayed less impairment on a variety of measurements and tasks compared to participants who abstained from alcohol. This study also provided evidence that these differences reflect mechanisms other than simple metabolic tolerance, or faster elimination of alcohol, in heavy drinkers.

Despite decades of work to evaluate the role of chronic tolerance in abuse potential, little is known about specific behavioral patterns that individuals demonstrate while intoxicated that could serve as risk factors for and/or markers of chronic tolerance and alcohol-related problems. One such mechanism is thought to be acute tolerance (Fillmore & Weafer, 2012). Acute tolerance to alcohol refers to a decreased response to the effects of alcohol observed during the time course of a single dose, independent of changes in blood alcohol concentration (BAC; Martin & Moss, 1993). Administration of a single dose of alcohol causes a sharp increase in BAC, which is referred to as the

ascending limb of the BAC curve. This is followed by a peak BAC and a subsequent gradual decrease, referred to as the descending limb. Acute tolerance was first described in a study conducted by Mellanby (1919) where it was observed that alcohol-induced ataxia in dogs was more severe during the ascending limb of the BAC curve compared to the descending limb, although the dogs' BACs were equivalent at these time points. Evidence of acute tolerance has since been identified in humans such that there is recovery in performance on behavioral measures and fewer subjective effects of intoxication at a given BAC on the descending limb compared with measures observed at the same BAC on the ascending limb (e.g. Beirness & Vogel-Sprott, 1984; Fillmore, Marczinski, & Bowman, 2005; Holland & Ferner, 2017).

Acute sensitivity to alcohol is another mechanism through which acute alcohol effects are thought to relate to at-risk drinking. Alcohol sensitivity refers to the intensity of an alcohol effect, and it is directly related to the development of heavy drinking behavior and, in turn, chronic alcohol tolerance (Gilman, Ramchandani, Crouss, & Hommer, 2012; Paulus et al., 2012; Schuckit & Smith, 1996). In general, research supports the notion that low levels of acute sensitivity to the effects of alcohol are associated with increased risk for alcohol abuse and dependence (Brumback, Dingcai, & King, 2007; Goldberg, 1943).

Moreover, individual differences in the acute effects (i.e., sensitivity and tolerance) of alcohol may predict at-risk drinking. In addition to impairment of function, some acute effects of alcohol could *directly* contribute to its abuse potential including its subjective and disinhibiting effects. This thesis examined further how acute sensitivity and tolerance to the subjective intoxicating and disinhibiting effects of a moderate dose

of alcohol relate to at-risk drinking. The following sections provide a review of what is known about the acute subjective and disinhibitory effects of alcohol and evidence for their relationship with abuse potential.

Subjective Intoxication and Acute Sensitivity

Alcohol produces a broad range of subjective effects (e.g., euphoria, sedation, stimulation, etc.). Subjective intoxication is assessed using self-report measures of perceived level of intoxication. One commonly used methodology is a visual analogue scale where participants rate their perceived level of intoxication on a scale ranging from 0, "not at all" to 100, "very much". These scales have been shown to be sensitive to the effects of alcohol such that individuals who consume more alcohol report greater impairment (e.g., Harrison & Fillmore, 2011). The intensity with which individuals experience subjective effects is linked to their drinking patterns and therefore implicated as a risk factor for AUD (Schuckit & Smith, 1996; Schuckit, Tsuang, Anthenelli, Tipp, & Nurnberger, 1996). Individual variability in sensitivity to the subjective effects of alcohol has been linked to abuse potential and other potentially dangerous behavior. For example, less sensitivity to subjective intoxication is associated with greater likelihood of driving while intoxicated (Quinn & Fromme, 2012; Roberts & Fillmore, 2017) as well as increased risky driving behavior (Laude & Fillmore, 2016). One laboratory study helped to further demonstrate this relationship by finding that DUI offenders typically self-report significantly lower subjective intoxication than a group of non-DUI offenders despite the fact that both groups were administered the same dose of alcohol and both showed significant impairment in ability to operate a driving simulator (Roberts & Fillmore, 2017). Further support for this relationship includes studies evaluating subjective

reactions to alcohol and drinking behavior in the adult offspring of alcoholics. This demographic is known to be at increased risk for the development of alcohol-related problems and was found to report less intense subjective reactions than individuals without a family history of alcohol problems (Pollock, 1992; Schuckit, 1988). Researchers posit that the decreased subjective intoxication in these individuals could potentially serve as a mediating factor in the relationship between familial alcohol abuse and later development of alcohol-related problems (Pollock, 1992; Schuckit, 1988).

Subjective Intoxication and Acute Tolerance

Studies have also examined the degree to which subjective intoxication displays acute tolerance over the course of a single dose of alcohol. A study by Martin and Earleywine (1990) found that, regardless of the rate of alcohol consumption, ratings for subjective intoxication recovered back to their baseline (or sober) levels sooner than did individuals' actual BACs. Acute tolerance to subjective intoxication is perhaps the most widely researched and well-established pattern of acute tolerance in the current literature likely because of the potentially dangerous implications this finding (i.e., perceiving oneself as less intoxicated than one actually is on the descending limb). Indeed, it seems that individual differences in acute tolerance to subjective intoxication might be especially linked to alcohol abuse potential and engagement in risky behavior (e.g. binge drinking, driving under the influence; Fillmore & Weafer, 2012; Portans, White, & Staiger, 1989; Quinn & Fromme, 2012). This relationship has been further probed by laboratory research assessing acute tolerance to the subjective effects of alcohol compared to certain behavioral measures for which alcohol impairs performance.

Laboratory research has compared patterns of acute tolerance in subjective intoxication to those demonstrated for other behavioral and cognitive measures, most often by comparing self-report ratings of intoxication at time points on the ascending and descending limb with performance on behavioral tasks conducted at the same time points. A recent review of such studies concluded that acute tolerance to subjective effects of alcohol is reliably demonstrated, whereas the effect for behavioral measures is more variable (Comley & Dry, 2020). These findings add to the potentially dangerous implications of acute tolerance to subjective intoxication by suggesting that, not only do individuals feel sober long before their BAC reaches zero, they also feel sober long before they regain complete control of certain alcohol-impaired behaviors.

In sum, the extant literature examining the relationship between abuse potential and the subjective effects of alcohol has demonstrated three critical findings. First, it provides evidence that sensitivity to subjective intoxication predicts abuse potential in that those who perceive themselves as less intoxicated are at increased risk. Second, the literature suggests that acute tolerance does not develop uniformly across different behaviors. Finally, it indicates that disparities in the rates of acute tolerance for different alcohol effects may be implicated in risky behavior, including at-risk drinking.

Differences in Acute Tolerance Among Behavioral Effects of Alcohol

In addition to acute tolerance to the subjective effects of alcohol, there is also evidence of acute tolerance in certain alcohol-impaired behavioral functions. For example, research shows that alcohol-induced slowing of reaction time recovers from the ascending to descending limb when measuring performance at equal BACs (Fillmore et al., 2005). In fact, reaction time has been shown to recover to baseline, or drug-free,

levels during the time course of a single dose of alcohol well before BAC declines to zero (Schweizer & Vogel-Sprott, 2008). However, other behaviors do not show the same pattern of recovery. Some complex cognitive functions, including error-monitoring and behavioral inhibition, do not display acute tolerance (Cromer, Cromer, Maruff, & Snyder, 2010; Marczinski, Stamates, & Maloney, 2018; Ostling & Fillmore, 2010; Schweizer & Vogel-Sprott, 2008; Weafer & Fillmore, 2012). Because of the rich literature linking behavioral disinhibition to substance use and abuse (e.g. Lee, Hoppenbrouwers, & Franken, 2019), researchers have largely focused on how the lack of acute tolerance demonstrated in this behavior might play a role in abuse potential.

Acute Sensitivity and Tolerance to the Disinhibiting Effects of Alcohol

There is evidence to suggest that sensitivity to alcohol's disinhibiting effects is strongly associated with abuse potential (e.g. Iacono, Malone, & McGue, 2008; Marczinski, Combs, & Fillmore, 2007). Alcohol acutely impairs one's ability to inhibit behavior such that increased quantities of alcohol consumed are associated with increased failure to inhibit behavioral reactions on laboratory tasks (Marczinski & Fillmore, 2005). Disinhibition is critical in terms of risk because failure to inhibit behavior is thought to, at least in part, account for many of the socially inappropriate or dangerous behaviors associated with alcohol intoxication (see, de Wit, 2009 for review). Individual differences in sensitivity to these disinhibiting effects are thought to be an important predictor of drinking habits. For example, laboratory research indicates that participants who are more sensitive to the disinhibiting effects of alcohol, as measured by performance on a cued go/no-go task, consume more alcohol when given ad libitum access (Weafer & Fillmore, 2008).

Performance on the cued go/no-go inhibitory control task is impaired in a dose-dependent fashion under alcohol, but does not typically demonstrate acute tolerance (Fillmore et al., 2005). Based on evidence that alcohol-induced disinhibition is associated with increased quantity consumed in a single drinking episode (Weafer & Fillmore, 2008), it has been theorized that poor recovery of inhibitory control (i.e., a lack of acute tolerance) may lead to binge drinking behavior. Lack of acute tolerance to disinhibition could compromise individuals' ability to discontinue their consumption, further perpetuating a drinking episode after it has begun (Fillmore, 2003; Fillmore & Weafer, 2012; Marczinski et al., 2007). This thesis assessed the possibility that individual differences in acute tolerance to alcohol-induced disinhibition predicts at-risk drinking.

Purpose

Most research on acute alcohol sensitivity and tolerance has concerned the overall magnitude of these effects averaged across participants with little attention to individual differences in the effects and how those differences might be related to abuse potential. In large part, this is due to limited sample sizes in laboratory studies that preclude examination of individual differences and their relation to measures of abuse potential. Prior research provides evidence that sensitivity to the effects of alcohol relates to abuse potential (Gilman et al., 2012; Paulus et al., 2012; Schuckit & Smith, 1996), and there is growing evidence that acute tolerance to certain alcohol-induced behavioral impairments might also play a role (Fillmore & Weafer, 2012; Marczinski et al., 2018). However, researchers have yet to compare their value as predictors of at-risk drinking and how they may interact to contribute to abuse potential. In order to evaluate individual differences in

acute sensitivity and tolerance as predictors of abuse potential, a larger sample size of participants is necessary.

The current thesis tested individual differences in acute sensitivity and acute tolerance to 0.65 g/kg alcohol on disinhibition and subjective intoxication in a large sample of young adult non-dependent drinkers in a placebo-controlled design. Data were aggregated over six separate studies to obtain a sufficiently large sample size to assess these individual differences and how they may relate to abuse potential. Broadly, the parent studies tested average acute sensitivity and tolerance on behavioral tasks and subjective intoxication among young adults. The resultant aggregate sample size (N = 200) allowed evaluation of specific responses to alcohol (i.e., subjective intoxication and disinhibition) that may be especially predictive of heavy drinking patterns indicative of at-risk consumption. It also allowed for assessment of which effect, sensitivity or acute tolerance, for each given measure was more important to at-risk drinking. In terms of sensitivity, I predicted that drinkers who were more sensitive to the disinhibiting effects of alcohol and less sensitive to its subjective intoxicating effect would be at-risk drinkers as indicated by self-reporting greater typical quantities of alcohol consumption per occasion. In terms of acute tolerance, I predicted that those who showed little or no acute tolerance to the disinhibiting effect and greater acute tolerance to the subjective intoxicating effect would drink more.

Method

Participants

An aggregate sample of young adult social drinkers was comprised of participants from six separate studies conducted in the investigators' laboratory. Participants (N =

200) were between 21 and 33 years old (M = 22.84, SD = 2.49) and were recruited from the community between 2005 and 2016 for participation in research projects assessing the acute effects of alcohol on behavioral and cognitive function (Fillmore, Blackburn, & Harrison, 2008; Fillmore et al., 2005; Fillmore & Weafer, 2012; Marczinski et al., 2007; Miller & Fillmore, 2014; Roberts, Monem, & Fillmore, 2016). Only studies with a common population, methodology and testing procedures were included. These criteria included young adult participants with no history of alcohol use disorder, counterbalanced, repeated dose design with two alcohol dose conditions (0.0g/kg and 0.65 g/kg), dose effect measurement following the same time course (ascending and descending limb of the BAC curve), common assessment of disinhibition and subjective and self-reported drinking patterns. Volunteers were excluded from participation if they self-reported a history of head trauma or other central nervous system injury. Potential participants were also excluded if they reported a psychiatric disorder or a substance use disorder. To further screen for alcohol use disorders the Short-Michigan Alcohol Screening Test (S-MAST; Selzer, Vinokur, & van Rooijen, 1975) was administered, and volunteers with a score of five or greater were excluded from participation. Volunteers who screened positive for recent drug administration using urinalysis were also excluded. No women who were pregnant or breast-feeding participated in the research, as was determined using self-report measures and urine human chorionic gonadotrophin levels. The aggregate sample was comprised of 88 women and 112 men. In terms racial make-up, participants self-identified as Caucasian (n =171), African American (n = 22), or as other (n = 7).

Measures

Disinhibition. A cued go/no-go reaction time task was used to measure participants' response inhibition to no-go targets and their reaction time to go targets \ (e.g., Fillmore & Weafer, 2004). The task required finger presses on a keyboard and measured the ability to inhibit prepotent behavioral responses of executing a key press. Cues (vertical and horizontal rectangles) provided preliminary information regarding the type of target stimulus (i.e., go or no-go) that was likely to follow, and the cues had a high probability of signaling the correct target. Participants were instructed to press the forward slash (/) key on the keyboard as soon as a go (green rectangle) target appeared and to suppress the response when a no-go (blue rectangle) target was presented. The go cue conditions were of particular interest. Go cues generate response prepotency which speeds response time to go targets. However, subjects must overcome this response prepotency to inhibit the response if a no-go target is subsequently displayed. Response inhibition was measured by the proportion of no-go targets in which subjects failed to inhibit a response (*p*-inhibition failures) during the test. Disinhibition was indicated by a higher proportion of inhibition failures (i.e., greater *p*-inhibition failure score). A test required approximately 15 minutes to complete. The task has been used in other research, has strong psychometrics, including reliability, and is highly sensitive to dose-dependent impairing effects of alcohol on drinkers' inhibitory control (Fillmore & Weafer, 2012; Weafer & Fillmore, 2016).

Subjective Intoxication. Participants rated their self-perceived level of intoxication using a 100 mm visual-analogue scale (VAS) ranging from 0, "not at all" to

100, “very much”. These scales have been shown to be sensitive to the subjective effects of alcohol (e.g., Harrison & Fillmore, 2011).

At-Risk Drinking. At-risk drinking was measured using the Personal Drinking Habits Questionnaire (Vogel-Sprott, 1992). This self-report questionnaire was used to sample participants’ typical drinking patterns, including consumption of excessive quantities of alcohol or frequent drinking. The PDHQ measured three aspects of participants’ current and typical drinking behavior including (1) frequency, or the typical number of drinking occasions per week, (2) dose, or milliliters of absolute alcohol consumed during a typical drinking episode per kilogram of body weight, and (3) duration, or typical time span (in hours) of a drinking occasion.

Procedure

Participants were recruited from the community using flyers, posters, online advertisements, and newspaper advertisements. All volunteers provided informed consent prior to participation, and all parent studies were approved by the University of Kentucky Medical Institutional Review Board. All participants were compensated for their participation.

Volunteers responded to advertisements by calling the laboratory and participated in a telephone screening procedure conducted by a research assistant. All eligible volunteers were told that the purpose of the study was to examine the effects of alcohol on behavior. All sessions were conducted at the Human Behavioral Pharmacology Laboratory at the University of Kentucky between the hours of 10 AM and 6 PM. Participants were required to abstain from alcohol for 24 hours prior to each session and fast for 4 hours prior to each session. Before testing sessions began, body weight was

measured, a BAC of 0.0 g/kg was verified using a breathalyzer [Intoxilyzer, Model 400 (CMI Inc., Owensboro, KY)], and urine samples were collected to ensure participants were negative for recent drug use and pregnancy.

Familiarization session. During the intake and familiarization session, participants were introduced to laboratory procedures and completed a practice session of the cued go/no-go task. Information regarding drug and alcohol use history, health status, and general demographic information was obtained using the Personal Drinking Habits Questionnaire (PDHQ) and the Short-Michigan Alcohol Screening Test (S-MAST).

Test sessions. Participants were tested on two separate occasions under different doses of alcohol, 0.0 g/kg (placebo) and 0.65 g/kg. Each session, including familiarization, was conducted on a different day separated by a minimum of one day and a maximum of seven days. The dose order was counterbalanced across participants.

During test sessions, participants received either a dose of 0.65 g/kg alcohol or a placebo dose of 0.0 g/kg. The size of the 0.65 g/kg dose was calculated based on participants' body weight and was equally divided into two glasses with each containing one part 96.4% alcohol and three parts carbonated mix. Participants were given two minutes to consume each drink, and the second beverage was served four minutes after consumption of the first. This dose has been shown to typically produce an average peak BAC of 80 mg/100 ml about 60 minutes after consumption and has been shown to impair inhibitory control and slow reaction time as measured by the cued go/no-go task (Fillmore et al., 2005). The placebo beverages contained four parts carbonated mix at an equal volume to the active dose. A small amount of alcohol (3 ml) was floated on the surface of the beverage before dividing it into two equal glasses. The glasses were

sprayed with an alcohol mist that resembled condensation and provided a strong scent of alcohol. Prior research indicates that participants believe these beverages contain alcohol (Fillmore & Vogel-Sprott, 1998). The timing of consumption of placebo beverages was identical to that of the active dose.

Following dose administration, the cued go/no-go task and VAS measure of subjective intoxication was administered at two time points. These tests corresponded to a comparable BAC for the ascending (test 1) and the descending (test 2) limbs of the BAC curve. Test 1 (ascending limb) occurred 25-35 minutes post-administration, and test 2 (descending limb) occurred 85-95 minutes after dose administration. To ensure this was the case, BAC was measured using a breathalyzer. Breath samples were also obtained at 60 minutes when peak BAC was expected. Because participants were recruited for the purpose of different studies, they also completed an additional task during test sessions, including a driving simulation task, a motor coordination task, a choice reaction time task, or a multi-sensory cued go/no-go task. However, these tasks were administered after the cued go/no-go task, so it is unlikely that go/no-go task performance would have been reactive. Participants remained in the lab until their BAC fell below 20 mg/100 ml, and transportation home by taxi was provided after the sessions. Upon completion of the final session, participants were paid and debriefed

Data Analyses

To confirm that disinhibition and subjective intoxication were sensitive to alcohol, paired-sample *t* tests compared alcohol and placebo on test 1 for each measure. Acute tolerance in a measure was tested by a 2 Dose (alcohol and placebo) x 2 Test (test 1 and test 2) analysis of variance (ANOVA).

Regression analyses tested the degree to which individual differences in sensitivity and acute tolerance predicted typical quantity of consumption. The magnitude of acute sensitivity and acute tolerance was calculated for each participant. Sensitivity magnitude scores were obtained by subtracting the participant's placebo response from the alcohol response during test 1. Magnitude scores for acute tolerance represented the difference between the sensitivity scores on test 1 and test 2 (see details in Results). For sensitivity, a multiple linear regression tested the degree to which sensitivity to the disinhibiting and subjective intoxicating effects separately and jointly accounted for individual differences in participants' typical quantity. For acute tolerance, a multiple linear regression tested the degree to which tolerance to the disinhibiting and subjective intoxicating effects separately and jointly accounted for individual differences in typical quantity. Regression models also explored the possibility that sensitivity and acute tolerance scores might also account for individual differences in participants' frequency of drinking.

Results

Drinking Habits

The sample reported a mean typical quantity of consumption of 4.9 drinks (*SD* = 2.4) and an average drinking frequency of 2.2 (*SD* = 1.1) days per week. The mean duration of their typical drinking occasion was 3.7 (*SD* = 1.3) hours, and the average number of months for which the participants reported drinking regularly was 71.5 months (6.0 years; *SD* = 34.3). Minimum and maximum values for each measure of drinking behavior are reported in Table 1.

Table 1

Descriptive Statistics of Participants' Drinking Habits

	Mean	SD	Minimum	Maximum
Frequency (days)	2.2	1.1	0.08	7.0
Quantity (drinks)	4.9	2.4	1.0	12.0
Dose (mg absolute alcohol/kg weight)	1.2	0.6	0.2	3.3
Duration (hours)	3.7	1.3	0.5	8.0
History (weeks)	71.5	34.3	5.0	195.0

Frequency = typical number of days alcohol consumed per week; Quantity = typical number of drinks consumed per drinking occasion; Dose = typical dose of alcohol consumed per drinking occasion; Duration = typical duration of drinking occasion; History = number of months alcohol consumed regularly.

Blood Alcohol Concentrations

The 0.65 g/kg alcohol dose produced a mean peak BAC of 80.6 mg/100 ml (*SD* = 14.3) 60 to 70 minutes post-administration. The mean BAC on test 1 (ascending limb) and test 2 (descending limb) was 70.4 mg/100 ml (*SD* = 20.0) and 71.5 mg/100 ml (*SD* = 13.2), respectively. A paired-sample *t* test revealed no significant difference in the BAC between test 1 and test 2, $t(199) = 0.8$, $p = 0.4$. There was no significant BAC difference between men and women at peak or during either test (*p*s > 0.2). No detectable BACs were observed during the placebo session.

Acute Sensitivity and Tolerance

Figures 1 and 2 plot the mean subjective intoxication and disinhibition scores on test 1 and test 2 following alcohol and placebo. Acute sensitivity to alcohol effects on subjective intoxication and disinhibition were tested by paired sample *t* tests that compared alcohol to placebo responses on test 1. As shown in Figure 1, subjective intoxication was significantly greater under alcohol, $M = 52.8$, $SD = 22.0$, compared with placebo, $M = 13.8$, $SD = 15.8$, $t(196) = 24.1$, $p < 0.001$. As shown in Figure 2, *p*-inhibition failure was also significantly greater under alcohol, $M = 0.30$, $SD = 0.32$, compared with placebo, $M = 0.25$, $SD = 0.34$, $t(199) = 4.5$, $p < 0.001$. Thus, alcohol reliably increased levels of subjective intoxication and disinhibition among the sample.

2 Dose x 2 Test ANOVAs tested for acute tolerance in each measure. For subjective intoxication, a significant main effect of dose was obtained, $F(1,191) = 644.2$, $p < 0.001$, and Figure 1 shows that subjective intoxication was greater in the alcohol condition during both tests. A dose x test interaction was also obtained, $F(1,191) = 59.4$, $p < 0.001$. Figure 1 shows that the interaction is due to acute tolerance to the subjective

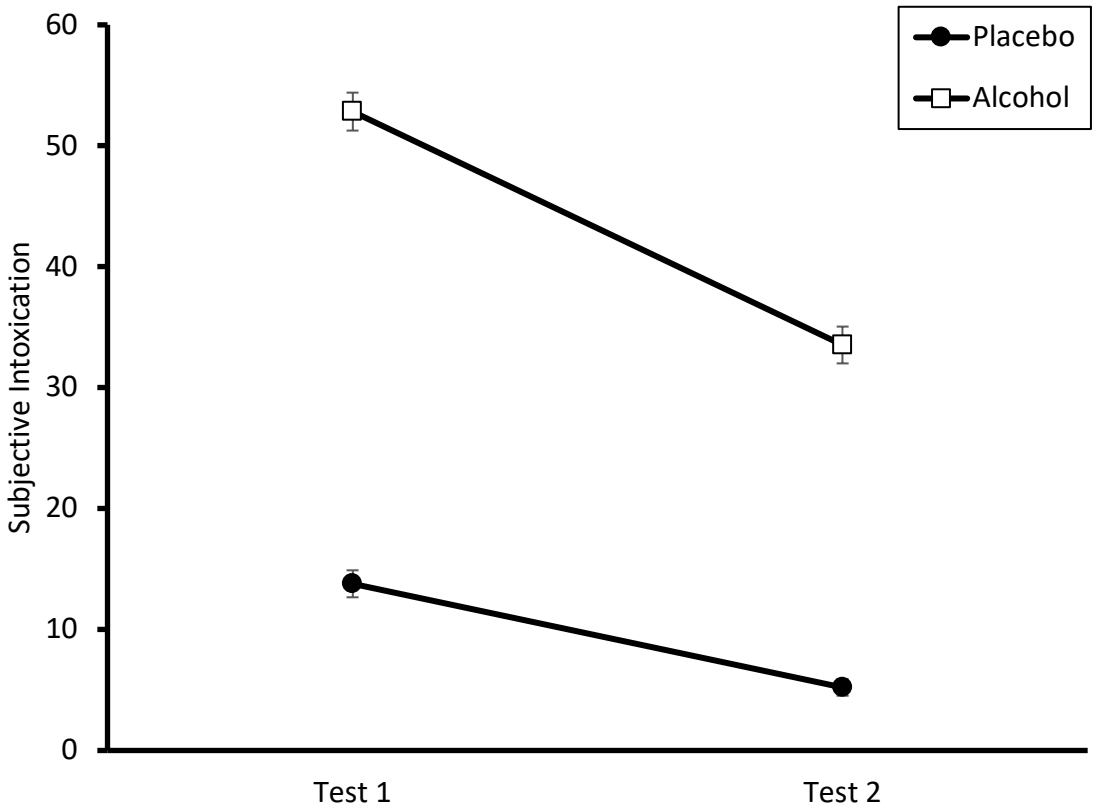

Figure 1. Mean subjective intoxication scores for tests 1 and 2 under the 0.0- (placebo) and 0.65-g/kg alcohol dose conditions. The *capped vertical lines* show the standard errors of the mean

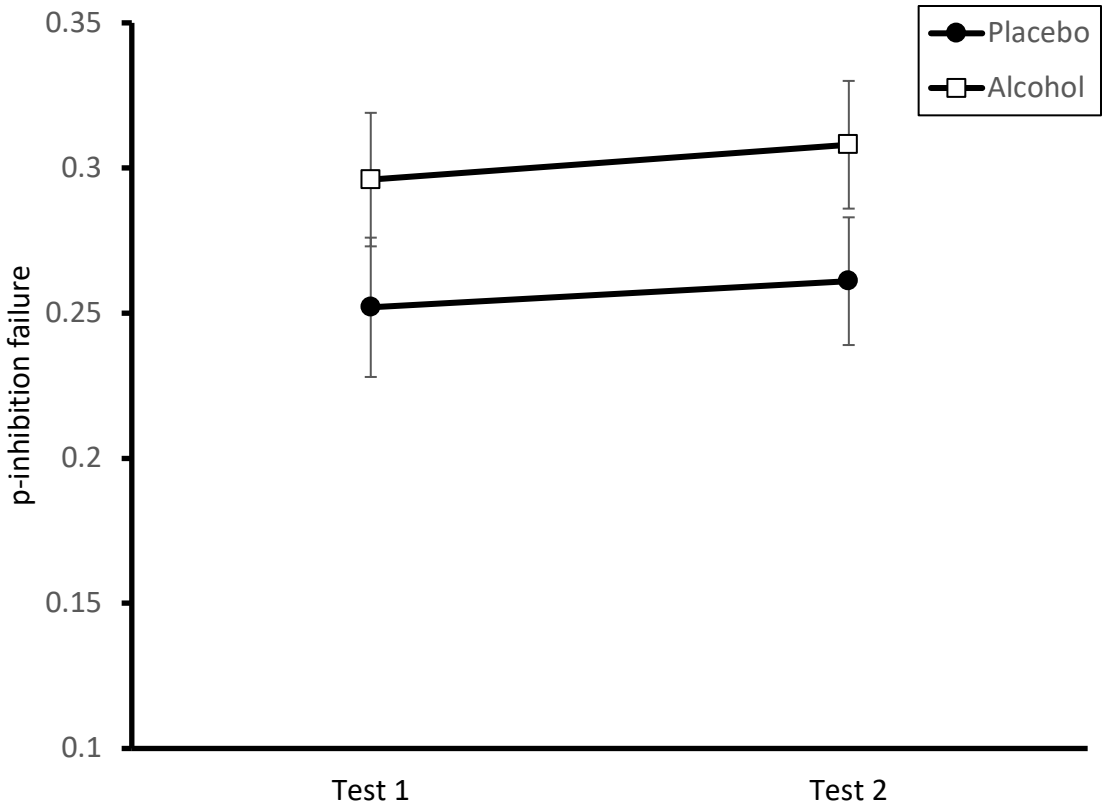

Figure 2. Mean *p*-inhibition failure for tests 1 and 2 under the 0.0- (placebo) and 0.65-g/kg alcohol dose conditions. The *capped vertical lines* show the standard errors of the mean

intoxicating effect of alcohol. Under alcohol, intoxication ratings decreased markedly from test 1 to test 2. By contrast, intoxication ratings showed little change across tests following placebo. For disinhibition, no significant dose x limb interaction was obtained ($p = 0.851$). However, there was a main effect of dose, $F(1, 198) = 32.8$, $p < 0.001$. Figure 2 demonstrates that disinhibition was greater in the alcohol condition compared to the placebo condition on both tests.

Acute Sensitivity as a Predictor of Drinking Habits

A multiple linear regression model tested the degree to which drinkers' acute alcohol sensitivity predicted their typical quantity of alcohol consumption. Acute sensitivity scores were calculated for each participant by subtracting the responses following placebo from the response following alcohol on test 1. Sensitivity scores were calculated for subjective intoxication and disinhibition, and higher scores indicated greater sensitivity to alcohol. The sensitivity scores for subjective intoxication and disinhibition were z-transformed to allow for their comparison as simultaneous predictors of typical quantity in a multiple linear regression equation.

The regression analyses of the sensitivity scores as predictors of typical quantity are presented in Table 2. Less sensitivity to subjective intoxication predicted greater typical quantity. Sensitivity to disinhibition did not predict typical quantity, nor did the interaction between scores. For drinking frequency, the only significant predictor was subjective intoxication whereby less sensitivity predicted greater drinking frequency, $\beta = -0.284$, $p < 0.001$.

Table 2

β-coefficients and Statistics Obtained from Simultaneous Regression of Sensitivity Scores to Subjective Intoxication and Disinhibition (i.e., p-inhibition Fails), and their Interaction Predicting Typical Quantity

Variable	*b*	*SE*	*t*	*p*
Subjective Intoxication (SI)	-0.414	0.174	-2.380	0.018*
Disinhibition	0.004	0.178	0.023	0.982
SI x Disinhibition	-0.152	0.206	-0.736	0.462

Quantity: R^2 = 0.029, adjusted R^2 = 0.014, *SE* estimate = 2.424, df = 192.
*Sig indicates a value of $p < 0.05$.

Acute Tolerance as a Predictor of Drinking Habits

Acute tolerance scores for subjective intoxication and disinhibition were generated for each participant in order to determine the degree to which acute tolerance to these effects predicted subjects' typical drinking quantity. To calculate these scores, the sensitivity scores for test 1 were subtracted from sensitivity scores for test 2; Sensitivity scores for test 2 were calculated using the same protocol explained above. The regression analyses of the acute tolerance scores as predictors of typical quantity are presented in Table 3. Acute tolerance to the subjective intoxicating and disinhibiting effect showed a significant interaction as predictors of subjects' typical quantity of alcohol consumption. Figure 3 plots this interaction. The figure shows that acute tolerance to the subjective intoxicating effects of alcohol moderated the relationship between acute tolerance to disinhibition and typical alcohol consumption. Low acute tolerance to disinhibition was associated with increased drinking in those who also showed low acute tolerance to subjective intoxicating effects. However, acute tolerance to the disinhibiting effects of alcohol did not predict consumption in those with high acute tolerance to subjective intoxication.

The same regression model assessed the relationship between acute tolerance scores and drinking frequency. Neither acute tolerance score nor their interaction predicted drinking frequency, $R^2 = 0.008$, $p = 0.694$.

Additional Analyses

Sex differences in sensitivity, acute tolerance, and their relationship with typical quantity were also assessed. Two-sample *t* tests were used to test sex differences in sensitivity and acute tolerance. Women were found to be more sensitive to subjective

Table 3

β-coefficients and Statistics Obtained from Simultaneous Regression of Acute Tolerance to Subjective Intoxication, Disinhibition, (p-inhibition Fails), and their Interaction Predicting Typical Quantity

Variable	*b*	*SE*	*t*	*P*
Subjective Intoxication (SI)	0.157	0.172	0.908	0.365
Disinhibition	0.314	0.201	0.116	0.120
SI x Disinhibition	0.468	0.228	2.048	0.042*

Quantity: $R^2 = 0.032$, adjusted $R^2 = 0.017$, *SE* estimate = 2.435 , df = 187.
*Sig indicates a value of $p < 0.05$.

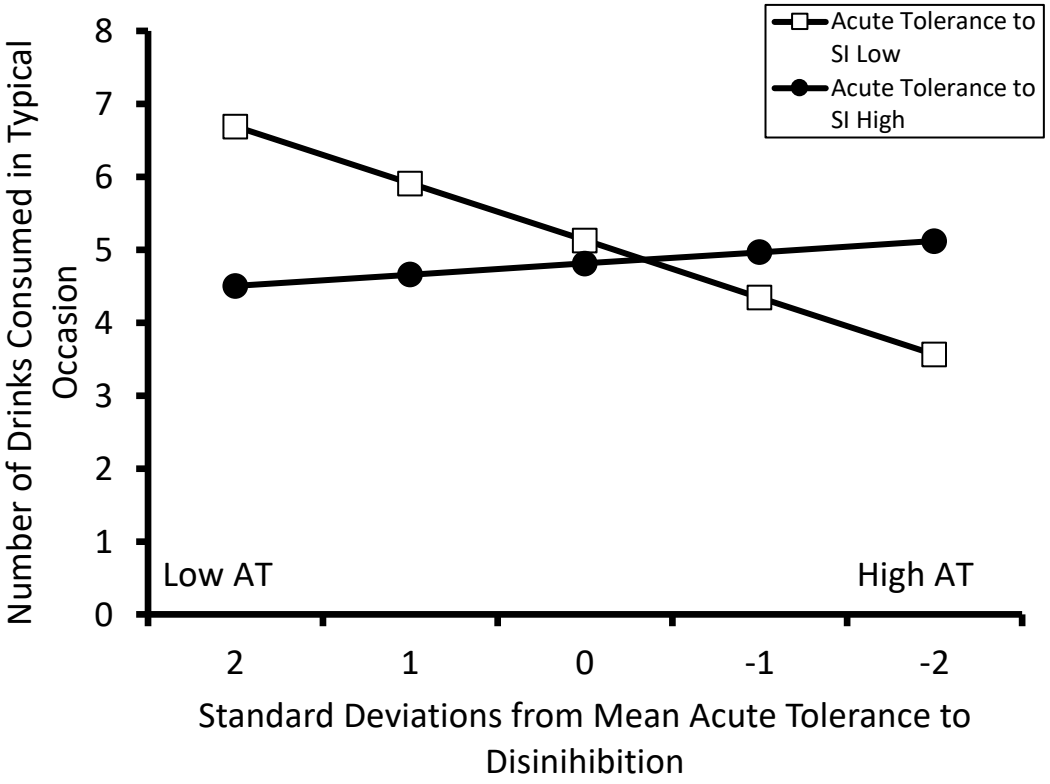

Figure 3. Regression lines relating typical quantity consumed to acute tolerance in disinhibition for those low and high on acute tolerance to subjective intoxication.

intoxication, $M = 44.5$, $SD = 20.8$, than men, $M = 34.9$, $SD = 23.6$, $t(194) = 3.0$, $p = 0.003$). No sex differences were found in acute sensitivity to the disinhibiting effects of alcohol nor acute tolerance on either measure ($ps > 0.08$). Additionally, there were no sex differences in the relationships of sensitivity or acute tolerance to subjects' quantity or frequency of consumption for either the subjective intoxicating or disinhibiting effect of the drug ($ps > 0.15$).

It is important consider the possibility that the observed increased disinhibition as measured by cued go/no-go task represents a speed-accuracy tradeoff. The speed-accuracy tradeoff is the phenomenon by which individuals' decreased accuracy on the task is a result of faster response times and reduced cognitive processing (Garrett, 1922). However, reaction time to both the go and no-go cue conditions were slower under alcohol compared to the placebo condition, although this difference was statistically significant only in the no-go condition, $t(199) = -5.8$, $p < 0.001$. Based on these findings, a speed-accuracy tradeoff is not a plausible explanation for the observed performance deficits under alcohol in our sample.

Discussion

This study examined how individual differences in the subjective intoxicating and disinhibiting effects of alcohol predict at-risk drinking behavior. By aggregating data across a several laboratory studies, a sufficient sample size allowed us to test the degree to which subjects' acute sensitivity and acute tolerance to these effects predicted at-risk drinking behavior. The study showed that 0.65 g/kg alcohol reliably increased levels of subjective intoxication and disinhibition among the sample. Low sensitivity to subjective intoxication was associated with heavier typical drinking quantities. For acute tolerance,

the interaction between subjective intoxication and disinhibition predicted drinking quantity. Heavier drinking was associated with low acute tolerance to disinhibition, especially for those who also showed low acute tolerance to subjective intoxication.

The relationship between reduced sensitivity to alcohol's subjective effects and increased drinking is consistent with prior research suggesting heavy drinkers show less sensitivity to the subjective effects of alcohol compared with light drinkers (Goldberg, 1943; King, de Wit, McNamara, & Cao, 2011).

With regard to acute tolerance, subjects' levels of subjective intoxication showed reliable recovery under alcohol over the 90-minute interval between test 1 to test 2. The recovery cannot be attributed to differences in BACs as the mean BACs at each test were nearly identical. By contrast, acute tolerance to the disinhibiting effect of alcohol was not reliably observed across the sample. Moreover, the large sample size allowed us to observe the marked individual differences in the degree of acute recovery from the disinhibiting effects. Indeed, some drinkers displayed pronounced recovery from the disinhibiting effect of alcohol between test 1 to test 2, while others showed an intensification in disinhibition over this interval. Acute tolerance was specifically predictive of heavier quantities of drinking but not greater frequency of consumption. Based on this specificity, it is posited sustained subjective intoxication and disinhibition under alcohol could additively contribute to continued drinking, leading to excessive binge use. Moreover, low acute tolerance to these effects may also increase risk for other potentially dangerous behaviors while drinking such as driving under the influence, aggression, and high-risk sexual behaviors.

Taken together, these results suggest a shift in the relative importance of the subjective and disinhibiting effects of alcohol across the time course of a drinking episode. On the ascending limb, reduced sensitivity to subjective intoxication is associated with heavy drinking. However, over the time course of a dose, it appears that sustained disinhibition becomes increasingly important in terms of predicting heavy drinking, especially for those who also have low acute tolerance to alcohol's subjective effects. These findings provide evidence that those who are most susceptible to overconsumption within a drinking episode are those with reduced sensitivity to subjective intoxication and reduced acute tolerance overall. The subjective and disinhibiting effects of alcohol have long been associated with at-risk drinking, and our findings further elucidate this relationship by suggesting that acute responses to these alcohol effects may be markers of abuse potential at different time points in a drinking episode. Individuals with reduced sensitivity to subjective intoxication are likely to consume greater quantities of alcohol early on in order to reach a desired level of intoxication, but as time goes on, alcohol-induced disinhibition appears be more important in heavy drinking as it perpetuates further alcohol consumption. The role of sustained disinhibition in predicting increased alcohol consumption appears to be especially important for those who also experience sustained subjective intoxication. These findings illustrate the importance of understanding the time course of multiple effects of a drug rather than focusing on a single time point or even the time course of a single effect.

The current study was the first to examine acute tolerance with a sample size of this magnitude. To our knowledge, this is also the first study to identify an interaction in

acute effects of alcohol that might be implicated in abuse potential and that different acute effects may be markers of at-risk drinking at different time points during a drinking episode. However, it is important to consider some limitations of the current study. First, the observations were limited to two test times over 90 minutes after dose administration. Therefore, our results only capture behavioral adaptations occurring in the first 90 minutes after alcohol consumption. Future studies may consider using intravenous alcohol administration in order to clamp BAC at the target level (e.g., 80mg/100ml) for a specified length of time (e.g., up to 3 hours; Huppert et al., 1998; Ramchandani, Bolane, Li, & O'Connor, 1999). This would allow for multiple tests within a session. Such additional tests may provide a clearer picture regarding the shift in relative importance of the subjective and disinhibiting effects of alcohol within a drinking episode. Furthermore, incorporating more test sessions may allow for exploratory analyses using mathematical models of acute tolerance growth (Radlow, 1994, 2006). Finally, the clamping procedure tightly controls participants' alcohol exposure, effectively reducing variability in BAC both between participants and within participants across tests.

It is also important to consider the generalizability of the results to problem drinkers. The current sample was comprised of social drinkers who had no history of alcohol use disorder (AUD), therefore caution should be taken in applying the findings to individuals with a history of alcohol abuse and dependence. However, the sample was comprised of young adults, many of whom reported regularly engaging in heavy drinking behavior. Over half (58%) of the sample reported that their typical quantity of consumption meets criteria for binge drinking (four or more drinks/episode for women and five or more drinks/episode for men). Binge drinking in adolescence and young

adulthood is associated with increased risk for later alcohol abuse (Viner & Taylor, 2007), so it is possible that the response profiles implicated in heavy drinking mediate this heightened risk. A final issue of consideration is the correlational nature of this study. The data are cross-sectional, barring any conclusions regarding the direction of the relationship between drinking habits and alcohol response profiles. Drinking habits may directly impact alcohol response in addition to other influences such as genetic factors, environmental factors, and personality characteristics. For example, it is plausible that reduced sensitivity among heavier drinkers within this sample is a marker of risk *or* a consequence of increased drinking that is indicative to greater chronic tolerance among these drinkers.

Results from this study shed light on how two different effects of alcohol that have long been linked to its abuse potential might interact to predict at-risk drinking behavior on an individual basis. These findings could also provide insight into how individual differences in alcohol responses and interactions of alcohol effects may be markers of, or perhaps directly contributing to, alcohol abuse potential. With this insight, we are one step closer to identifying brain substrates involved in the relationship between acute alcohol effects and at-risk drinking. Based on our findings, perceiving oneself as less intoxicated on the ascending limb, and low acute tolerance overall appear to be especially related to increased abuse potential. Identification of these response patterns that may serve as markers of abuse potential can inform future research that uses advanced imaging and brain stimulation techniques (i.e., transcranial magnetic stimulation [TMS]) to help uncover the neural mechanisms involved in heavy drinking and binge drinking behavior. In addition to providing guidance for future research evaluating brain

substrates, these results highlight the importance of assessing acute responses to alcohol on several effects and how these effects may be dynamic across the time course of a drinking episode.

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